

SEPTICÆMIA DUE TO  
GRAM-NEGATIVE BACILLI\*D. S. MUNROE, M.D. and  
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SEPTICÆMIA due to bacteria of the coliform and related groups of organisms is seen not infrequently in a general hospital, yet there are relatively few reports of this condition in the literature. This paper is concerned with septicæmia due to Gram-negative bacilli of the coliform, *Pseudomonas* and *Proteus* groups.

Felty and Keefer<sup>1</sup> in 1924 reported a series of cases of sepsis due to *Escherichia coli* and in 1951 Waisbren<sup>2</sup> published an excellent report on bacteræmia due to Gram-negative bacilli. The latter reported that approximately 40% of the positive blood cultures in a general hospital were due to this group of organisms, and in the vast majority of these cases the genito-urinary tract appeared to be the origin of infection.

In the Vancouver General Hospital during the years 1951, 1952 and 1953, 33% of the positive blood cultures were due to organisms of this group. It is the purpose of this report to give our experiences with regard to the finding of these positive blood cultures and to analyse the cases in an attempt to elucidate the clinical features, associated diseases and treatment. It is realized that the use of the findings of a routine bacteriological laboratory to indicate the frequency of these infections may give a grossly false impression because the blood cultures were taken at the discretion of a large number of clinicians. In spite of this objection, however, our figures do indicate that, contrary to not infrequently expressed opinion, septicæmia due to Gram-negative bacilli is quite common and quite important.

Whether the condition under review should be called septicæmia or bacteræmia is debatable. Some of our cases may well have had only a bacteræmia, but neither the clinician nor the bacteriologist can determine this with any certainty on the basis of a positive blood culture. The clinician must act on the assumption that he is dealing with a septicæmia. We have therefore decided that septicæmia is the preferable

term, and certainly this is so when treatment is to be considered.

## METHODS AND MATERIAL

The cases were those of 44 patients who had one or more positive blood cultures in the laboratory at the Vancouver General Hospital during the period January 1951 to December 1953. In the routine technique for taking the blood cultures 10 to 12 c.c. of venous blood was collected in a citrate bottle and, in the laboratory, a poured plate was made using 2 c.c. of blood with 40 c.c. of blood agar base. The remainder of the specimen was split between two 50 c.c. tubes of dextrose brain broth containing 0.1% agar. Arterial culture has rarely been attempted and none is included in this series. Antibiotic sensitivity tests were carried out by the disc method and sulfonamide sensitivity tests were done using Mueller Hinton medium containing 10 mgm. % sodium sulfadiazine. The aureomycin solution for the discs was made up to 100 mcg. per ml. in pH 3 buffer and the streptomycin and chloramphenicol solutions contained 500 mcg. per ml. The medium used for these tests was usually nutrient agar and the plates were incubated at 30° C. for 18 hours. Using 6 mm. filter paper discs, any strain showing a zone of inhibition of 12 mm. diameter or more was called relatively sensitive. On the sulfonamide medium the absence of growth from a light inoculum was used as the criterion of sensitivity.

Table I presents an analysis of all blood cultures taken at the Vancouver General Hospital for the three-year period. It will be seen

TABLE I.

BLOOD CULTURES  
(VANCOUVER GENERAL HOSPITAL—1951, 1952 AND 1953)

	1951	1952	1953	Total	% positive
Total blood cultures taken . . .	715	960	1,098	2,773	—
Total positive blood cultures . .	36	43	54	133	4.8%
Total positive blood cultures due to enteric Gram-negative bacilli— 44 cases* . . . . .	10	12	23	45	1.6%

\*From the Departments of Medicine and Bacteriology, Vancouver General Hospital. Presented to the North Pacific Society of Internal Medicine, Spokane, Washington, March 1954.

\*One patient had a septicæmia due to two types of Gram-negative bacillus.

that 1.6% of all blood cultures taken during this period yielded enteric Gram-negative bacilli. It is also clear from this table that 33% of all the positive blood cultures were due to this group of organisms.

Table II shows a breakdown of the etiological organisms. The striking thing in this table is the recent increase in incidence of septicæmia due to *Proteus*.

TABLE II.

Organism	1951	1952	1953	Total
<i>E. coli</i> . . . . .	5	5	5	15
<i>A. aerogenes</i> . . . . .	4	1	3	8
Paracolon . . . . .	0	2	2	4
<i>Ps. pyocyanea</i> . . . . .	0	1	2	3
<i>Proteus</i> . . . . .	1	3	11	15
Total . . . . .	10	12	23	45

\**Salmonella* and *Bacteroides* not included.

\*\*One patient had septicæmia due to two types of Gram-negative bacillus.

SENSITIVITY TO ANTIBIOTICS

The strains of *E. coli* and the paracolon bacilli were more sensitive to antibiotics than the other organisms in Table II. Table III shows a summary of these tests.

With this technique for determining sensitivity of the strains, chloramphenicol inhibited more organisms than did any other antibiotic. This is more marked with the strains of *Proteus*, 50% of which were sensitive to chloramphenicol.

No mention has been made in the table of the effect of polymyxin, mainly because our *in vitro* tests have often been difficult to read. However, the clinical use of this drug in pyocyanus infections has been encouraging.

The percentages given in Table III refer only to the strains of organisms isolated in this series of blood cultures. However, the figures, with the

TABLE III.

Organism	No. of strains tested	Percentage of strains sensitive to			
		Aureomycin	Chloramphenicol	Streptomycin	Sulfadiazine
<i>E. coli</i> . . . . .	15	55	92	77	85
<i>A. aerogenes</i> . . . . .	8	50	64	37	50
Paracolon . . . . .	4	50	75	75	75
<i>Ps. pyocyanea</i> . . . . .	3	0	33	33	33
<i>Proteus</i> . . . . .	15	0	50	7	7

exception of those for the *Pseudomonas* group, fall fairly well into line with what we have found when dealing with a much larger number of strains isolated from urine and other clinical material. Most *Pseudomonas* strains appear to be sensitive to polymyxin and almost half of them also to sulfonamides, while a lesser number of strains have been inhibited *in vitro* by the other antibiotics.

TABLE IV.

Organisms	Number of patients with positive blood cultures			
	1951	1952	1953	Total
<i>Staph. pyogenes</i> . . . . .	8	11	8	27
<i>Staph.</i> (coagulase-negative) . . . . .	0	3	5	8
<i>M. tetragenus</i> . . . . .	0	0	1	1
<i>Strep. pyogenes</i> . . . . .	1	3	1	5
<i>Strep. faecalis</i> . . . . .	0	0	1	1
<i>Strep. viridans</i> . . . . .	2	4	2	8
<i>Strep.</i> (anaerobic) . . . . .	1	0	2	3
<i>D. pneumoniae</i> . . . . .	3	2	3	8
<i>N. meningitidis</i> . . . . .	5	3	2	10
<i>H. influenzae</i> . . . . .	2	1	3	6
<i>Bacteroides</i> . . . . .	4	1	0	5
<i>Salm. typhi</i> . . . . .	1	2	4	7
<i>Salm. paratyphi</i> . . . . .	0	1	0	1
Unidentified Gram-negative bacillus . . . . .	0	0	1	1
Total . . . . .	27	31	33	91

Table IV shows the numbers of patients with positive blood cultures for other organisms in the same period. It is of interest that there were almost as many positive blood cultures for the organisms under study in this paper (45) as there were for all types of staphylococci and streptococci (53).

PORTAL OF ENTRY

The portal of entry of the bacteria into the blood stream was the urinary tract in over one-half of the cases (59%). The next most common portal of entry was the female genital tract

(11%). Suppurating wounds were the portals of entry in 3 cases (7%). In two cases a similar organism was recovered not only from the urine but also from another focus in each (female genital tract in one case and tracheotomy wound in one case). The biliary tract was believed to have been the portal of entry in one case and the umbilical cord may have been the portal in one case.

The portal of entry was unknown in 5 cases (11%). Four of these patients had blood dyscrasias, there being one case each of lymphatic leukæmia, aplastic anæmia, thrombocytopenic purpura and multiple myeloma. In the other patient with blood dyscrasia in the series (agranulocytosis due to aminopyrine) the portal of entry was the urinary tract.

#### PRECIPITATING CAUSE

The precipitating cause of the septicæmia was unknown in most of the cases. Some at least of the abortions were criminally induced and presumably this was the precipitating cause in these cases. In six of the cases in which the urinary tract was the portal of entry, the septicæmia developed within one week of transurethral operation on the prostate or bladder. Several other patients had had operations on the urinary tract but not directly related in time to the development of septicæmia. That transient bacteræmia frequently follows transurethral prostatic resection was shown by Biorn *et al.*<sup>3</sup> In their series of cases, none developed septicæmia. It is generally recognized, however, that septicæmia may occasionally be precipitated by transurethral prostatic resection.

#### CLINICAL FEATURES

The clinical features of septicæmia due to the organisms under discussion vary tremendously. The patient's condition varies from one of utmost urgency and gravity to that of a low-grade, indolent, subacute illness. The tempo of the illness may be fulminating, with death in a few days, or the patient may go on for weeks with ultimate recovery. Twenty-eight of our patients were males, 16 females.

The febrile response is very variable. The illness is frequently ushered in with a series of rigors, one or more per day, or the patient may have a sustained fever of low or high grade which may continue for days. Ultimately, most

patients will have at least one rigor. In our series, 75% had at least one rigor, the hallmark of a septicæmia. It is to be noted, however, that rigors may be absent throughout a comparatively long febrile course with resultant dimming of diagnostic suspicions. In fact, one of our patients who died from his septicæmia had a fever on one day only, several days before death. Petechiæ were not seen in any of these cases.

Shock is not uncommonly the most striking clinical feature of septicæmia due to Gram-negative bacilli. This has recently been emphasized by Waisbren,<sup>2</sup> by Wise, Shaffer and Spink,<sup>4</sup> by Braude *et al.*<sup>5,6</sup> and by Stevens *et al.*<sup>7</sup> from the University of Washington School of Medicine. Wise, Shaffer and Spink reported that 8 of 53 patients with positive blood cultures due to Gram-negative bacilli had severe hypotension and shock. The etiological bacteria were *A. aerogenes* in 3 cases, *E. coli* in 2, *Proteus* in 1, paracolon bacilli in 1, and *Salmonella typhimurium* in 1. Six of the 8 patients ultimately succumbed. Braude *et al.* have reported 4 similar cases of severe shock with 3 deaths.

The severity of the shock following transfusion with blood contaminated by Gram-negative bacilli has been stressed in papers by the Seattle group,<sup>7</sup> by Braude *et al.*<sup>5,6</sup> and by Borden and Hall.<sup>8</sup>

When we reviewed the protocols in our cases, severe hypotension and tachycardia were frequently noted and in several instances much effort was expended in trying to determine the cause of the shock-like state and in attempts to alleviate it. It was frequently very difficult to determine to what extent the septicæmia was the cause of the hypotension because of complicating factors such as other associated disease or the sudden onset of auricular fibrillation or presence of an obviously terminal state.

Excluding all these cases, there were 10 cases in which, apart from septicæmia, no factor which could have produced the shock-like state was present. In these cases the blood pressure was recorded, in different individuals, as between 50 and 90 mm. Hg systolic for appreciable periods of time up to several days. This hypotension usually was associated with a tachycardia. Five of this group were young (age 31-40), and five were old (age 69-78). All recovered.

Table V shows a list of associated conditions. Some patients had more than one associated dis-

TABLE V.

ENTERIC GRAM-NEGATIVE BACILLARY SEPTICÆMIA (44 CASES)	
Associated conditions	No. of cases
Structural abnormality of urinary tract . . . . .	20
Abortion . . . . .	6
Pregnancy at term . . . . .	2
Blood dyscrasia . . . . .	5
Diabetes mellitus . . . . .	5
Cirrhosis of liver . . . . .	2
Other . . . . .	6

ease (e.g., diabetes mellitus and necrotizing papillitis) while, in other cases, the portal of entry was clearly due to a urinary infection without structural disease or abnormality of the urinary tract.

Apart from urinary infection, which was present in every case in which the urinary tract was the portal of entry, the structural abnormalities in the urinary tract included benign prostatic hypertrophy, carcinoma of the prostate, carcinoma of the bladder, renal calculi, pyonephrosis and necrotizing papillitis. The five blood dyscrasias were composed of one case each of chronic lymphatic leukæmia, aplastic anæmia, multiple myeloma, thrombocytopenic purpura and agranulocytosis due to aminopyrine. All five patients with diabetes had associated urinary infection and two were proved to have necrotizing papillitis at operation or autopsy.

Bulbar poliomyelitis was the basic disease in one patient. The portal of entry in this case was an infection either of the urinary tract or of the tracheotomy wound. Both of these sites yielded the same organism as was present in the blood stream. Staphylococcal septicæmia was associated in two cases, and pneumonia, carcinoma of the stomach, carcinoma of the pancreas and subacute bacterial endocarditis (due to *Streptococcus faecalis*) were the associated diseases in one case each. One patient (an infant of six days) had meningitis due to *E. coli*. Mitral stenosis was an associated but unrelated disease in one case.

Seven patients in this series developed metastatic septic foci due to their septicæmia. These foci were widespread abscesses in one case, lung abscesses in three cases, abscess of myocardium in one case and splenic abscess in one case; these six patients died. The seventh patient developed a vertebral abscess in which cure ultimately was achieved.

The mortality in this series was 35%. The mortality was 86% in those with metastatic foci and 80% in those with blood dyscrasias. Table VI shows the essential features of the fatal cases. It will be noted that most of these patients had serious organic disease and that in two of the cases staphylococcal septicæmia was also present. Autopsy was done on all except one.

TREATMENT

The treatment of septicæmia due to Gram-negative bacilli may be considered under three general heads.

1. *Specific treatment.*—The choice of antibiotic is frequently difficult in infections of this nature as the organisms involved show marked differences in their *in vitro* responses to antibiotics. The *in vitro* response is the best guide we have and in our opinion it is a fairly reliable one. Based on this series of cases, chloramphenicol would appear to be the most likely antibiotic to succeed in a case of Gram-negative bacillary septicæmia. However, the sensitivity tests are often only a relative indication of the effectiveness, and other broad spectrum antibiotics such as aureomycin and terramycin have often been used successfully either in large doses or intravenously. Sulfadiazine is frequently of great value, as indicated in Table III.

Some cases were seen that did well on penicillin and streptomycin which were started before the results of the blood cultures were known. However, it is felt that in these instances streptomycin was the effective agent. Penicillin alone rarely influences infections of this type. It is evident that, as we are dealing with a condition whose course even when untreated is not predictable, we are unable to be dogmatic about the treatment of choice. Moreover, at times certain strains of Gram-negative bacilli may predominate in an institution just as do the staphylococci, and treatment pending specific bacterial studies of the case should be based on local experience and the above generalizations.

2. *The treatment of shock.*—This is similar to the treatment of shock in other situations and includes the use of blood plasma, plasma expanding solutions, oxygen, cortisone, and pressor agents. Norepinephrine (noradrenaline) is believed to be of considerable value in this regard but was rarely used in this series of cases.

3. *Drainage of a septic focus.*—This might include cervical dilatation and uterine curettage,

TABLE VI.

ENTERIC GRAM-NEGATIVE BACILLARY SEPTICÆMIA (44 CASES). MORTALITY TABLE:						
Sex	Age	Organism	Diseases present	Portal of entry	Autopsy	Comment
F.	42	<i>E. coli</i>	Cirrhosis liver. Chronic infective hepatitis. Urinary infection. Acute hæmorrhagic pancreatitis.....	Ur. tract	Yes	
M.	75	<i>A. aerogenes</i>	Ca. stomach with biliary obstruction. Liver abscess. Diabetes. Necrotizing papillitis.	Ur. tract	Yes	
M.	70	<i>E. coli</i>	Hypertensive heart disease. Benign prostatic hypertrophy.....	Ur. tract	No	Died 3 days after TUPR*.
M.	62	<i>E. coli</i>	Chronic lymphatic leukæmia.....	Unknown	Yes	
F.	31	<i>E. coli</i>	Aplastic anæmia. Retroperitoneal hæmorrhage.....	Unknown	Yes	
M.	81	<i>A. aerogenes</i>	Arteriosclerotic heart disease. Staphylococcal septicæmia. Pyæmic abscess myocardium. Benign prostatic hypertrophy.....	Ur. tract	Yes	Blood culture positive 2 days after TUPR.
M.	70	<i>Proteus</i>	<i>H. influenzae</i> pneumonia. Multiple lung abscesses.....	Unknown	Yes	
M.	67	<i>A. aerogenes</i>	Acute heart failure. Prostatic hypertrophy. Left renal calculus.....	Ur. tract	Yes	
M.	75	<i>Proteus</i>	Old myocardial and cerebral infarction. Chronic pyelonephritis. Early aortic bacterial endocarditis.....	Ur. tract	Yes	
M.	72	<i>Proteus</i>	Old ca. penis (amputated). Recent resection metastatic inguinal nodes Thrombophlebitis with pulmonary embolism.....	Wound	Yes	
M.	69	<i>A. aerogenes</i>	Ca. prostate with metastases. Pyonephrosis. Abscess spleen.....	Ur. tract	Yes	Blood culture positive 16 days after TUPR.
F.	28	<i>Proteus</i>	Pregnancy at term. Bulbar poliomyelitis. Tracheotomy. Widespread abscesses.....	Ur. tract or wound	Yes	
M.	64	<i>Proteus</i>	Multiple myeloma. Subacute bacterial endocarditis due to <i>S. faecalis</i> .....	Unknown	Yes	
M.	69	<i>E. coli</i>	Thrombocytopenic purpura.....	Unknown	Yes	Cholecystectomy and splenectomy 18 days before.
M.	70	<i>Proteus</i>	Staphylococcal septicæmia. Benign prostatic hypertrophy. Lung abscesses.....	Ur. tract	Yes	

\*TUPR = transurethral prostatectomy.

or incision and drainage of an abscess, or ureteral catheterization, or even nephrectomy in a case that has failed to respond to adequate antibiotic therapy. That the drainage or removal of a septic focus is of the utmost importance is exemplified by the following brief case report.

#### CASE REPORT

Mrs. A.R. was a known diabetic of several years' duration. She had been reasonably well, although almost blind and quite deaf, until the day before admission to hospital, when she developed a severe pain in the left lower quadrant of the abdomen. She was clear mentally on admission to hospital but when first seen

by one of us (D.S.M.) a few hours later she was unconscious. Examination brought forth nothing of note except pin-point pupils and very slow respirations. A few hours later she was again clear mentally and it was felt that she had had a reaction to morphine which had been given.

Soon after awakening, patient had a rigor with temperature elevation to 104.5° F. Her diabetes was adequately controlled. The urine showed pyuria and, after taking a blood culture, treatment was begun with penicillin and streptomycin. The blood culture yielded a paracolon bacillus, as did the culture of the urine. The organism was sensitive to streptomycin, aureomycin, aureomycin and chloramphenicol, and sulfonamide.

The patient had another rigor on the day after admission and on the following day cystoscopy and retrograde pyelography were done by Dr. John Balfour. No dye excretion was noted from the left ureter. The left pyelogram showed much disorganization of the renal

pelvis and a large cavity replacing the inferior major calyx. The right pyelogram was normal and kidney function on the right was normal. The probable diagnosis was thought to be necrotizing papillitis.

The patient's condition showed some slight improvement in the next two days but the response was considered inadequate. Streptomycin was stopped and aureomycin intravenously in large doses begun. She became progressively worse and six days after admission a left nephrectomy was done by Dr. Balfour. The kidney showed acute and chronic pyelonephritis, papillitis necrotans and septic thrombosis of the renal vein. Cultures of the pelvis of this kidney revealed paracolon bacillus.

The patient's condition was immediately and dramatically improved. Antibiotic therapy was continued for some time. She was discharged apparently well six weeks after admission. Two months later she was re-admitted to hospital with destructive lesions of the bodies of the 11th and 12th dorsal vertebræ and of the disc between. This had been the cause of local pain for the preceding two weeks. Needle biopsy revealed purulent material but it was sterile to culture. The pathological diagnosis on this material was chronic osteomyelitis. The patient was treated on a Bradford frame and was given aureomycin. The lesion was cured in nine months after the date of the second admission.

#### COMMENT

The variety of diseases with which Gram-negative bacillary septicæmia may be associated and the frequency of the condition make the subject one of practical importance at the present time. Perhaps the most important fact is that if penicillin alone is used as preliminary treatment in cases of suspected septicæmia, it will fail in one-third of these cases because of the insensitivity of the enteric organisms. It is therefore strongly recommended that all cases of possible septicæmia, after a blood culture has been taken, should be treated with an antibiotic which usually is effective against enteric organisms as well as against the more common Gram-positive cocci. If penicillin is to be used, it must not be used alone but in conjunction with an antibiotic which is known usually to be effective against Gram-negative bacilli. This is especially important if the patient is in shock, if he has any disease of the urinary tract, if he has had a recent operation on the urinary tract or if he is a diabetic. More precise antibiotic therapy can be ordered when definitive bacteriological studies are at hand.

Contamination of blood with Gram-negative bacilli has come to be recognized as one of the three great hazards of blood transfusion, the other two being homologous serum jaundice and incompatibility of blood. With modern blood banks, contamination of this type may, it is said, be expected in 1 to 3% of transfusions. In any case, the presence of a rigor during a transfusion with subsequent shock should lead to investigation of this possibility and to immediate specific antibiotic treatment.

#### SUMMARY

1. An analysis has been made of 44 cases of Gram-negative bacillary septicæmia occurring in a three-year period at the Vancouver General Hospital. These cases constitute 33% of the total cases of septicæmia which occurred in the same period.

2. The bacteriological and clinical data have been reviewed. The portals of entry and associated diseases have been noted.

3. Treatment has been discussed. Because of the frequency of this type of septicæmia, it has been recommended that, at least until precise bacteriological diagnosis has been made, the treatment of all cases of suspected septicæmia should include an antibiotic which is known to be effective against Gram-negative bacilli in most instances.

4. It has been noted that serious or even fatal reactions occur from transfusion of blood contaminated by Gram-negative organisms.

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#### THE HUMP IS NOT FOR WATER

Does the camel have a special compartment in his stomach or hump for storing water? The answer to this old puzzler is no.

That is what two scientists found out in the Sahara desert. They were particularly interested in determining how the camel manages to survive in the hot, dry regions that mean death to most other creatures.

They learned that camels hardly ever sweat at all, even in extreme heat. This "stinginess" with body moisture enables them to go for months without a drink. One of the experimental camels subsisted for 17 days on nothing but hay and dried dates out in the scorching sun where the temperature often exceeded 100° F. But when a camel does drink, it can tank up in a hurry. One moisture-starved animal downed 30 gallons within ten minutes.